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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/307,640	09/16/94	FERGUSON	M 39-148

HM12/0816

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EXAMINER	
CUNNINGHAM, T	
ART UNIT	**PAPER NUMBER**
1644	24

DATE MAILED: 08/16/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
08/307,640	Ferguson et al.
Examiner	**Group Art Unit**
Thomas Cunningham	1644

☐ Responsive to communication(s) filed on _____ .

☒ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *56-71* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *56-71* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

1. Claims 56-71 are active. The amendment filed 6/3/99 (Paper No. 23, Amendment H) is considered below.

2. A distinguishing property of TGF-β3 discussed in the recent interview is its disclosed ability to induce non-fibrotic growth, compared to other forms of TGF-β like TGF-β1 and 2 which may help wounds heal, but which cause fibrosis. The prior patent to Ferguson et al., U.S. 5,662,904 describes the importance of neutralizing TGFβ1 and TGFβ2, but not TGFβ3. Limitation of the instant claim language to exclude the presence of fibrotic growth factors such as TGF-β1 and 2 would expedite examination.

3. Independent claims 57 and 64 have been amended to recite "consisting essentially of" TGF-β3. The claim phrase "consisting essentially of" excludes ingredients that would "materially affect the basic and novel characteristics" of the claimed composition. In re Herz, 537 F.2d at 551, 190 USPQ at 463; In re Janakirama-Rao, 317 F.2d at 954, 137 USPQ at 895.

4. (Withdrawn) The prior rejection of claims 57, 58, 60, 65, 66 and 68 (and claims depending from these claims) are rejected under 35 U.S.C. 112, second paragraph as failing to particular point out and distinctly claim the invention in the recitation of the term "anti-fibrotic agent" is withdrawn in view of Applicant's comments.

5. (Maintained) Claims 56-71 are rejected under 35 U.S.C. 112, first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

A. The specification does not provide adequate guidance as to which molecules are anti-fibrotic because it would require undue experimentation to identify such functionally-defined agents--see rejection under 35 U.S.C. 112, second paragraph above. Claims limited to antibodies that specifically neutralize the fibrotic activities of TGFβ1 and TGFβ2, or other known molecules

which interfere with the activities of these specific fibrotic growth factors and do not neutralize the anti-fibrotic growth factor activity of TGFβ3 would not be subject to this rejection.

--Applicant's comment on page 4 that claims 56, 62, 63, 64, 70 and 71 do not refer to antifibrotic agents and should not have been rejected has been considered, but is not persuasive as these claims encompass the use of fibrotic agents. It is incumbent upon the examiner to reject independent claims along with dependent claims reciting specific limitations that though not recited by the independent claim are embraced by it.

B. The specification does not adequately describe so as to enable ribozymes or oligonucleotides that result in anti-fibrotic activity. For instance, in claims like claims 58 and 66 there is insufficient guidance as to which molecules are "fibrotic growth factors" as whether or not a particular molecule is a growth factor must be determined on a molecule-by-molecule basis and this involves undue experimentation due to the complexity of the cellular milieu and multifunctional nature of TGFβ functional activity which depends on the influences of other growth factors present at the site of wound healing. Claims limited to products which specifically inhibit the fibrotic activities of TGFβ1 and TGFβ2 and do not substantially inhibit the antifibrotic growth factor activity of TGFβ3 would not be subject to this rejection.

--Applicant urges that the instant claims are method, not composition claims, and therefore more latitude should be permitted for functionally-defined ingredients such as "anti-fibrotic agents". This is not persuasive as the anti-fibrotic agents are essential active ingredients used within the claimed methods and Applicant has not adequately described or enabled a genus of products with the requisite function. Anti-fibrotic agents do not share a conventional structure, neither can their specific identities be determined without undue experimentation.

C. Assuming arguendo, that the claims are limited to specific and known fibrotic growth factors, such as TGFβ1 and TGFβ2, there is no evidence of record that it is possible to transfect cells with agents such as ribozymes or antisense nucleic acid that suppress expression of such factors. Prima facie, one would expect that cells at the site of a wound would be surrounded or express numerous nucleases that would degrade ribozymes and nucleic acids prior to their uptake by cells expressing fibrotic factors. Thus, such agents would not reasonably be expected to penetrate such cells and diminish expression of the fibrotic factors they express. Evidence that uptake of such products would be expected to occur in healing tissue would obviate this rejection.

--Evidence that ribozymes and oligonucleotides exert anti-fibrotic activity would help obviate this rejection.

D. Assuming arguendo that such products would internalize and modulate intracellular protein expression it would be unpredictable what effects such agents would have on fibrosis and wound

healing. Such products would be expected to inhibit both fibrotic and antifibrotic factors so long as they had enough sequence similarity with the oligonucleotide or ribozyme product and thus with one another. For instance, antisense nucleic acids or ribozymes that bind to TGFβ1 and TGFβ2 (that have fibrotic activities) would also be expected to bind to TGFβ3 (which has antifibrotic activity) due to sequence similarities within this family of molecules. Limitation of the claim language to products which do not significantly affect TGFβ3 would help address this rejection.

--Evidence that ribozymes and oligonucleotides function within the claimed method would obviate this rejection.

6. Claims 56, 62, 63, 64, and 70-71 are rejected under 35 U.S.C. 103(a) as being unpatentable Cerletti et al, EP 0 433 225 (1990). A similar rejection has been previously set forth in section 5 of the last office action.

Cerletti et al. teach a method for treating wounds using TGFβ like proteins. The compositions disclosed by Cerletti et al. would be expected to comprise TGFβ3 as well as other TGFβ proteins.

Cerletti et al. do not teach the anti-fibrotic growth activity of TGFβ3.

However, the instant claim language does not exclude use of compositions comprising TGFβ3 in combination with other TGFβ proteins as taught by Cerletti et al. Page 9 of Cerletti et al. discloses different modes and manners of administration of TGFβ like proteins for wound healing.

One with ordinary skill in the medical and pharmaceutical art at the time of invention would have been motivated to use TGFβ like factors comprising TGFβ3 for the purpose of enhancing would healing and would have been motivated to select concentrations and modes of application following page 9 of the cited reference that would have minimized fibrosis at the would site.

Exclusion of fibrotic factors like TGFβ1 and TGFβ2 from the instant claim language would address this rejection. Claims reciting combination of TGFβ3 with an antifibrotic agent are not rejected as Cerletti et al. does not provide motivation for addition of an antifibrotic agent.

--Applicant urges on page 6 of the last response that the amended claim language addresses this rejection. This argument is not persuasive because the language "consisting essentially of" does not exclude use of compositions comprising TGFβ3 in combination with other TGFβ proteins as

taught by Cerletti et al. Exclusion of fibrotic factors like TGFβ1 and TGFβ2 from the instant claim language would address this rejection.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thomas M. Cunningham, Ph.D., J.D., whose telephone number is (703) 308-3968. Dr. Cunningham can generally be reached Monday through Thursday from 7:30AM to 6:00 PM. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

TC

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